Enhanced selectivity towards melanoma cells with zinc(II)-Schiff bases containing imidazole derivatives

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Streszczenie

Zinc(II)-complexes with the general formula [Zn(L_2)] containing 8-hydroxyquinoline Schiff bases functionalized with 1-(3-aminopropyl)imidazole or 1-(3-aminopropyl)-2-methyl-1*H*-imidazole on 2-position and their respective ligands (**HL^1** or **HL^2**) were synthesized and characterized by NMR, UV-Vis, FTIR and CD spectroscopies as well as ESI-MS spectrometry. Single crystals of **HL^2** and **$[Zn(L^1)_2]_n$** were analysed by SC-XRD. **$[Zn(L^1)_2]_n$** shows a 1D polymeric chain structure of alternating Zn(II) cations and bridging Schiff base ligands, in contrast to previously reported monomeric structures of analogous complexes. DFT calculations were performed to rationalize the polymeric X-ray structure of **$Zn(L^1)_2$**. Results showed that the ligands can bind as bi- or tridentate to Zn(II) and there is the possibility of a dynamic behavior for the complexes in solution. Both ligands and complexes present limited stability in aqueous media, however, in the presence of bovine serum albumin the complexes are stable. Molecular docking simulations and circular dichroism spectroscopic studies suggest binding to this protein in close proximity to the Trp213 residue. Biological studies on a panel of cancer cells revealed that the Zn(II)-complexes have a lower impact on cell viability than cisplatin, except for triple-negative breast cancer cells in which they were comparable. Notwithstanding, they display much higher selectivity towards cancer cells *vs.* normal cells, than cisplatin. They induce the generation of ROS and DNA double-strand breaks, primarily through apoptosis as the mode of cell death. Overall, the novel Zn(II)-complexes demonstrate improved induction of apoptosis and higher selectivity, particularly for melanoma cells, compared to previously reported analogues, making them promising candidates for clinical application.